REMARKS

Amendment of the Claims

Claims 1-30 are currently pending. Claims 19-26 are withdrawn pursuant to a restriction requirement.

Remaining independent claims 1 and 27 are amended to recite that the at least one effector molecule is a PEG or PEG derivative and the antibody fragment is a Fab' fragment with one or two cysteines in the hinge region. The basis for this amendment can be found at claims 1, 18, and 20 of the application as originally filed and at page 5, lines 3-4 of the specification. Claim 8 has been amended to clarify that the cysteine referred to in the light chain region is an engineered cysteine. Claim 28 is amended to be consistent with amended claim 27. Claims 29 is amended to recite that each effector molecule is PEG.

It is respectfully submitted that these amendments are sufficient to overcome all the rejections of the claims, for the reasons set forth more fully below.

Sequence Requirements

In response to the "Sequence Requirements" section at page 3 of the Office Action, and the "Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures" sent with the Office Action, applicant submits herewith a document entitled "RESPONSE TO NOTICE TO COMPLY MAILED MARCH 5, 2008 SEQUENCE LISTING STATEMENT." It is respectfully submitted that the amendment to the specification and the sequence listing submitted therewith are sufficient to meet the requirements of the Office with respect to the sequence listings of this application.

Specification

The specification also has been amended to recite the fact that the applicant is claiming the benefit under 35 USC 371 of International Application No. PCT/GB04/002870, having an international filing date of 01 July 2004 and claiming a priority date of 01 July 2003.

As the information concerning the benefit claim was previously submitted within the time period set forth in 37 CFR 1.78(a), and was recognized by the Office

as shown by its inclusion on the filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required, as per the first full paragraph on page 4 of the Office Action.

Claim rejections – 35 USC § 102

The rejection of claims 1-7, 10-13, 15-18, 27-28, and 30 as anticipated by Carter as evidenced by Rodrigues et al. and Bodmer et al. is respectfully traversed. Claims 1 and 27 are now amended to recite that the at least one effector molecule attached to the fragment is either PEG or a derivative thereof. None of Carter, Rodrigues, or Bodmer discloses a PEG or PEG derivative as an effector molecule.

The rejection of claims 1-18 and 27-30 as anticipated by Humphreys as evidenced by Rodriguez also is respectfully traversed. Humphreys is concerned with the production of antibody fragments, particularly dimeric $F(ab')_2$ fragments, containing the hinge sequence TCPPCPXYCPPCPA. Humphreys also describes the PEGylation of such fragments (Claim 8 and P.24 lines 8-24 (PEGylation of a $F(ab')_2$ containing hinge 2o 'TSDKTHTCPPCPATCPPCPA')). Thus, the over-riding emphasis in Humphreys is on antibody fragments with a hinge sequence containing **four** cysteines.

Humphreys also discloses, in the Examples, non-PEGylated Fab' fragments in which the interchain cysteines have been replaced with serines and in which the hinge sequences contain one or two cysteines. These fragments are included purely as experimental comparators for the fragments containing **four** cysteines which are the unequivocal subject of the invention described in Humphreys. Humphreys contemplates only that the Fab'and $F(ab')_2$ fragments containing **four** cysteines should be PEGylated (Claim 8); in the Examples (P.24 lines 8-24), only a $F(ab')_2$ containing the hinge sequence TSDKTHTCPPCPATCPPCPA was actually PEGylated.

It is noteworthy that in Humphreys the comparator Fab' fragments containing only one or two cysteines in the hinge were not PEGylated and that no suggestion was made to do so.

Thus Humphreys does not disclose an antibody fragment containing all the limitations of claim 1 or 27 as amended, and the rejection under 35 USC 102(b) has been overcome.

Double Patenting

The double patenting rejection over Humphreys U.S 6,642,356 in view of Humphreys WO 99/15549 is respectfully traversed.

At the time of the priority date of the present invention, one skilled in the art would not have attempted to attach PEG (or a derivative) to the hinge region of Fab' fragments containing only one or two cysteines in the hinge because of the risk that the PEG would draw water away from the antibody fragment, creating a destabilizing effect on the fragment that would force the heavy and light chains apart. Indeed, the fact that corresponding Fab' fragments were not PEGylated in the Humphreys reference(s) would only have served to add to these reservations and make the skilled person even more cautious, such that the prior Humphreys references is teaching one skilled in the art away from the present invention.

Surprisingly, and contrary to the perception in the art, the present inventors were able to demonstrate that even when an antibody Fab' fragment lacking the interchain disulphide is PEGylated, the heavy and light chains remain associated with each other and the PEGylated antibody Fab' fragment has equivalent antigen binding and *in vivo* activity compared to PEGylated Fab' fragments in which the interchain disulphide is present (See for example, Figure 11). In view of this surprising discovery, the invention as claimed herein would not have been obvious to one of ordinary skill in the art at the time the invention herein was made.

Statement of Common Ownership

The invention of the present application and U.S. 6,642,356 were, at the time the invention of the present application was made, owned by Celltech R&D Limited. It is respectfully submitted that the foregoing statement is sufficient to preclude a rejection under 35 U.S.C. 103(a) based upon the '356 patent as a reference under 35 U.S.C 102(e), (f), or (g), per MPEP § 706.02(l)(2).

As all points of rejection have been overcome, a Notice of Allowance is respectfully requested.

Respectfully submitted,

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/Sandra B. Weiss/
Sandra B. Weiss
Registration No. 30,814

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606-6709
Telephone: 312-913-0001
Facsimile: 312-913-0002